REMARKS

Status of the Claims

Claims 1-8, 10, 12 and 14-35 are currently pending in the application. Claims 1-7, 10, 12 and 28-36 stand rejected. Claims 8 and 14-27 are withdrawn as being drawn to a non-elected invention. Claims 1-5, 10, 12, 28-31 and 33-35 have been amended. Claim 36 has been cancelled. All amendments and cancellations are made without prejudice or disclaimer. No new matter has been added by way of the present amendments. Specifically, the amendment to claims 1-4, 28-30 and 33 are supported by the specification at, for instance, page 10, line 25 to page 11, line 4, page 19, lines 4-19, page 20, lines 18-21, and page 35, lines 16-18. Claims 5, 10, 12, 31, 34 and 35 have been amended to be consistent with the amendments to claims from which they depend. Reconsideration is respectfully requested.

ENTRY OF AMENDMENTS

The amendments to the claims should be entered by the Examiner because the amendments are supported by the as-filed specification and do not add new matter to the application. Additionally, the amendments should be entered since they comply with requirements as to form, and place the application in condition for allowance. Further, the amendments do not raise new issues. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-7, 10, 12, 28-36 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. (*See*, Office Action of December 21, 2007, at pages 2-3 and pages 10-11, hereinafter, "Office Action"). Claim 36 has been cancelled, thereby obviating the rejection of claim 36. Applicants traverse the rejection as to the remaining claims.

The Examiner states that the phrase "the method for preparing a cytotoxic lymphocyte in the absence of fibronectin" in claim 33 lacks antecedent basis.

Applicants have amended claim 33 to recite, in part, "as compared to that of a method for preparing a cytotoxic lymphocyte in the absence of at least one fibronectin fragment."

The Examiner also states that claim 1 is indefinite because it recites a method for "preparing" a cytotoxic lymphocyte which only includes a single active step of "expanding."

Although Applicants do not agree that claim 1 is indefinite, to expedite prosecution, claim 1 has been amended to recite, in part, "A method for expanding cytotoxic lymphocytes ..."

Finally, at paragraph 14 of the Office Action, the Examiner states that claims 1 and 28-30 are indefinite because the phrase "within each of the groups of" is unclear in its meaning. The Examiner states that it is unclear how a single polypeptide might comprise only one substitution and yet requires a substitution as described in parts (a)-(f) which may be more than one substitution. Further, the Examiner states that it is unclear whether in option (a) all glycines and alanines in the entire sequence be substituted or every glycine be substituted for an alanine, or only one glycine and one alanine be substituted for some other amino acid, etc.

Although Applicants do not agree that claims 1 and 28-30 are indefinite, to expedite

prosecution, the claims have been amended to remove the phrases upon which the Examiner bases the rejections, thereby obviating the rejection.

The Examiner states that claim 33 is also indefinite for reciting "expansion ratio." However, Applicants believe that the term "expansion" used in the context of tissue culture is sufficiently clear to one of skill in the art. Applicants further note that the claims have been amended to be directed to a method of expanding cytotoxic lymphocytes. Applicants believe these amendments address the Examiner's concerns about the term "expansion ratio."

The Examiner has not provided any independent reasoning to support the rejection of dependent claims 2-7, 10, 12, 31, 32, 34 and 35. Thus, dependent claims 2-7, 10, 12, 31, 32, 34 and 35 are believed to be definite for, *inter alia*, depending from a definite base claim, amended claims 1, 28-30 and 33.

Reconsideration and withdrawal of the indefiniteness rejection of claims 1-7, 10, 12, 28-35 are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 10, 12 and 28-35 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement and further because the specification, while being enabling for: a method for preparing cytotoxic lymphocytes in the presence of fibronectin or a fibronectin fragment comprising at least one of the amino acid sequences of SEQ ID NOS: 1 to 19, does not reasonably provide enablement for: a method for preparing cytotoxic lymphocytes in the presence of a fibronectin fragment, or a fibronectin fragment having a substitution, deletion, insertion, or addition to one or more amino acids. Claim 36 also stands

rejected under 35 U.S.C. § 112, first paragraph, for reciting new matter. (*See*, Office Action, at pages 3-6, and 11). Claim 36 has been cancelled, thereby obviating the rejection of claim 36. Applicants traverse the rejection as to the remaining claims.

The Examiner states that Applicants have not provided sufficient written description or enablement support to show Applicants had possession of (knowledge of) all possible fragments of fibronectin encompassed by the scope of the presently claimed invention, especially fragments of fibronectin having an unlimited number of substitutions, deletions, insertions or additions.

The Examiner indicates at page 5 of the Office Action, first full paragraph, that the term "functional equivalent" is unclear. The Examiner states that there is no function to which the equivalency is related. Additionally, the Examiner states that the phrase "at least one of the amino acid sequences" might encompass partial sequences of SEQ ID NOS:1-19.

Although Applicants do not agree that the claims lack written description support or enablement support, to expedite prosecution, the claims have been amended to clarify that the at least one fibronectin fragment comprise those "wherein the fibronectin fragment is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 19." Further, the claims no longer recite "functional equivalent." Additionally, the phrase "at least one of the amino acid sequences" has been amended to recite commonly accepted language for reference to sequence identifiers.

By the above amendments, Applicants have canceled claim 36, and the limitation of the number of culture days is added to each of claims 1, 28, 29, and 30.

Claims 1, 28, 29, and 30 of the present application are also amended to recite that the cells, such as peripheral blood mononuclear cells, are cultured in the presence of IL-2.

New Matter

Although claim 36 has been cancelled, the limitations of claim 36 have been added to claims 1 and 28-30. Thus, regarding the LAK cells and the Examiner's belief that the present claims should be limited to only "LAK" cells if the claims recite the limitation of "from 2 to 15 days," Applicants respectfully direct the Examiner's attention to the present specification, at page 4, lines 6-10, which discloses the following: "The lymphokine-activated killer cell (LAK cell) is a functional cell population having an cytotoxic activity, which is obtained by adding IL-2 to peripheral blood (peripheral blood leukocyte), umbilical cord blood, tissue fluid or the like containing lymphocytes, and culturing the cells in *vitro* for several days."

In addition, the present specification discloses at page 35, lines 4-9, the following: "The culture of LAK cell is carried out by incubating a cell which can be formed into LAK cell together with IL-2 in the presence of the above-mentioned effective ingredient. The cell which can be formed into LAK cell includes, but not particularly limited to, for instance, peripheral blood mononuclear cell (PBMC), Natural Killer (NK) cell, umbilical cord blood mononuclear cell, hematopoietic stem cell, blood components containing these cells, and the like."

In other words, by the above amendments, the culture step recited in the claims of the present invention is essentially directed to expansion of LAK cells as described in the specification. That is, Applicant shave clearly defined "LAK cell" such that the present claims are commensurate in scope with this definition. Therefore, no new matter is believed to be recited in the present claims, at least based on the presently submitted amended claims.

Therefore, reconsideration and withdrawal of the written description and enablement rejection of claims 1-7, 10, 12 and 28-35 are respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-6, 10, 12 and 28-35 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Pollok et al., *J. Virol.* 72:4882-4892, 1998 (hereinafter, "Pollok et al."). (*See*, Office Action, at pages 6-7). Applicants traverse the rejection.

The Examiner states that Applicants' specification refers to expanding a cell alternatively as also culturing a cell. The Examiner refers to pages 34-35 of the present specification to provide evidence that the expansion step is not limited, so long as fibronectin or a fragment thereof is in the cell culture with the cytotoxic lymphocyte.

However, according to the section of Pollok et al. entitled: "Retroviral Transduction Protocol," found on page 4883, right column, Pollok et al. only disclose that: (1) PBMCs were stimulated with IL-2, an anti-CD3 antibody, or an anti-CD3 antibody and an anti-CD28 antibody, (2) thereafter these cells were harvested, and the harvested cells were transformed with a retrovirus in the presence of a recombinant fibronectin fragment and IL-2 for 4 hours, and (3) the transformed cells were further harvested, washed, and cultured in a plate immobilized with an anti-CD3 antibody and an anti-CD28 antibody in the presence of IL-2. In other words, the fibronectin fragment was used for only 4 hours during the transformation, so that one can not conclude that expansion of the cells was carried out in the presence of the fibronectin fragment. At the very least, it is clear that incubation with fibronectin did not occur for 2 to 15 days, as presently claimed.

That is, although Applicants do not agree that Pollock et al. disclose all of the limitations of the presently claimed invention, to expedite prosecution, claims 1 and 28-30 have been amended to recite, in part, "wherein said culturing is performed for 2-15 days."

By the above amendments, since the culturing in the presence of a fibronectin fragment is performed for 2 to 15 days, the present invention is clearly distinguishable from that described in Pollok et al. Thus, Pollok et al. can not anticipate the presently claimed invention because Pollok et al. do not disclose all of the limitations of the presently claimed invention. Anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*See*, *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1990), quoting *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Dependent claims 2-6, 10, 12 and 31-35 are not anticipated as, *inter alia*, depending from a non-anticipated base claims, claims 1 and 28-30.

Reconsideration and withdrawal of the anticipation rejection of claims 1-6, 10, 12 and 28-35 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Ostergaard et al., Taguchi et al. and Nunclon

Claims 1-6, 10, 12, 28-30 and 33-35 remain rejected under 35 U.S.C. § 103(a) as being unpatentable as obvious over Ostergaard et al., *European J. Immunol.*, 25:252-256, 1995 (hereinafter, "Ostergaard et al.") in view of Taguchi et al., U.S. Patent No. 5,198,423 (hereinafter, "Taguchi et al.") as evidenced by Nunclon product information, VWRLabshop, page 1 (hereinafter, "Nunclon"). (*See*, Office Action, at pages 7-9). Applicants traverse the rejection.

The Examiner states that Applicants' previous arguments were based on limitations that are not recited in the claims. The Examiner cautions that arguments differentiating the presently claimed invention from the prior art must be based on limitations positively recited in the claims, i.e. the claims do not require incubation for periods longer than 4 hours. Furthermore, the Examiner contends that since the cited references disclose the single active step in claims 1 and 28-30, that of culturing cytotoxic lymphocytes in the presence of fibronectin, the cited references must inherently achieve the same results, even though they do not report the increase in IL-2 receptor expression or CD8 T cell ratio.

As already commented above, claims 1 and 28-30 have been amended to recite that the culture time is from 2 to 15 days. Furthermore, the claims have been amended to clarify that the cells subjected to the culturing step are limited to "peripheral blood mononuclear cells, NK cells, umbilical cord blood mononuclear cells, hematopoietic stem cells or blood components containing these cells."

Ostergaard et al. disclose that cytotoxic T cell (CTL) activity is enhanced by culturing the CTL clones in the presence of fibronectin, and that culturing is performed only for 4 hours, for the measurement of the CTL activity. Thus, Ostergaard et al. fail to disclose or suggest all of the limitations of the presently claimed invention, at least as recited in amended claims 1 and 28-30.

Furthermore, the secondary references of Taguchi et al. and Nunclon fail to cure the defects of the Ostergaard et al. disclosure. That is, these secondary references also do not, when considered in combination with Ostergaard et al., disclose or suggest all of the limitations of the presently claimed invention, especially as recited in amended claims 1 and 28-30.

Further, the effects of the method for expansion of cytotoxic lymphocytes of the presently claimed invention lead to the following important properties: a significantly improved expansion ratio, increased expression of IL-2 receptor, and an improved ratio of $CD8^+$ T cells. Ostergaard et al. do not disclose or suggest that such important effects can be achieved by culturing such cells for only 4 hours.

According to Ostergaard et al., at the sections entitled: "2.1 cloned CTL lines and antibodies" and "2.3 CTL degranulation," found on page 253, left-hand column, the cells that are subjected to culture are clones of CD8-positive CTLs, and the cells obtained by culturing these clones are all CD8-positive cells. Therefore, the improvement in the ratio of the CD8-positive cells achieved by the presently claimed invention would not be expected from the methods disclosed by Ostergaard et al.

In view of the above, even if Ostergaard were combined with Taguchi et al. or Nunclon, the presently claimed invention would not be obvious therefrom because the expansion disclosed in the presently claimed invention is clearly different from the methods of culturing in the presence of the fibronectin disclosed in Ostergaard et al.

Thus, reconsideration and withdrawal of the obviousness rejection of claims 1-6, 10, 12, 28-30 and 33-35 are respectfully requested.

Mizobata et al. and Taguchi et al.

Claims 1-7, 10, 12, 28-30 and 33-36 stand additionally rejected under 35 U.S.C. § 103(a) as being unpatentable as obvious over Mizobata et al., *British J. Cancer.*, 74(10):1598-1604, 1996 (hereinafter, "Mizobata et al.") in view of Taguchi et al. (*See*, Office Action, at pages 11-

12). Claim 36 has been cancelled, thus obviating the rejection of claim 36. Applicants traverse the rejection as to the remaining claims.

The Examiner states that Mizobata et al. disclose expansion of PBMC in the presence of anti-CD3 antibodies and human fibronectin which is immobilized on a tissue culture plate. The Examiner notes that PBMC contain cytotoxic lymphocytes and therefore meets this limitation of claims 1 and 28-30.

As disclosed in Mizobata et al. on page 1598 right hand column to page 1599, left hand column, the cells used in this reference are T cells having an antigen specificity for a specific tumor cell induced by co-culturing PBMCs with the autologous tumor cells. Mizobata et al. disclose that the tumor antigen-specific T cells obtained in the manner described above are cultured for 3 days in the presence of IL-2, an anti-CD3 antibody, and fibronectin. In other words, the cells that are cultured in the presence of fibronectin are not blood cell components *per se,* such as PBMCs, but are lymphocytes having an antigen specificity to tumor cells which is artificially induced by placing them in the presence of the tumor cells.

In contrast, by the above-described amendments of claims 1 and 28-30, the presently claimed cells that are cultured in the presence of at least one fibronectin fragment are limited to "peripheral blood mononuclear cells, Natural Killer (NK) cells, umbilical cord blood mononuclear cells, hematopoietic stem cells or blood components containing these cells."

By the above amendments, even if Mizobata et al. were combined with Taguchi et al., disclosing the fibronectin fragment of SEQ ID NO: 12 of the present invention, the presently claimed invention, as recited in at least amended claims 1 and 28-30, is not obvious in light of the combined disclosures of the cited references.

Since no specific reasoning is provided for the rejection of dependent claims 2-7, 10, 12 and 33-35, these dependent claims are believed to also be non-obvious for, *inter alia*, depending from non-obvious base claims, amended claims 1 and 28-30.

Thus, reconsideration and withdrawal of the obviousness rejection of claims 1-7, 10, 12, 28-30 and 33-35 are respectfully requested.

Rejections Under the Obviousness-Type Double Patenting Doctrine

Claims 1-7, 10, 12 and 28-36 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-8, 14-15, 24-25 and 28 of copending Application No. 10/486,512 in view of U.S. Patent 5,198,423 and Chen et al., 1994, and are further rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 20-21 of copending Application No. 10/568,745. (*See*, Office Action, at pages 9-10). Since the present application was filed before either of the cited co-pending applications, the Examiner is respectfully requested to hold the provisional rejections in abeyance until allowable subject matter is identified in the present application, according to the procedure described in M.P.E.P. § 804(I)(B)(1):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.
>
> If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without

need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue. If both applications are filed on the same day, the examiner should determine which application claims the base invention and which application claims the improvement (added limitations). The ODP rejection in the base application can be withdrawn without a terminal disclaimer, while the ODP rejection in the improvement application cannot be withdrawn without a terminal disclaimer.

Accordingly, the Examiner is respectfully requested to issue a Notice of Allowance in this case and to address any possible double patenting issues in the co-pending applications.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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